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(54) Title: **NITROOXYDERIVATIVES OF CYCLOOXYGENASE-2 INHIBITORS**

(57) Abstract: New compounds able to release COX-2 inhibitors and NO having formula (I): M-T-Y_A-NO₂ (I) for the treatment and/or prophylaxis of inflammatory processes.

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INTERNATIONAL SEARCH REPORT

International Application No
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A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07C323/49 C07C317/22 C07D231/12 C07C311/08 A61K31/235
A61K31/415

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07C C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 09948 A (NICOX SA) 12 March 1998 (1998-03-12) page 7, lines 1-15; pages 23-25, V Acl-Ac5; page 31, line 8 - page 33, line 2; page 38, line 21 - page 42, line 22; page 45, line 6 - page 49, line 15 idem	1,2,5, 11,12, 14,15, 19-23
Y		1,2,5, 11-13, 20-23
Y	WO 96 25405 A (G.D. SEARLE & CO) 22 August 1996 (1996-08-22) cited in the application page 2, lines 4-8; example 1 ----- -/-	1,2,5, 11-13, 20-23

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
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- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *Z* document member of the same patent family

Date of the actual completion of the international search

12 January 2004

Date of mailing of the international search report

23. 01. 2004

Name and mailing address of the ISA

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Van Amsterdam, L

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/06502

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>US 5 994 381 A (J. HARUTA ET AL) 30 November 1999 (1999-11-30) cited in the application example 2; column 34, line 65 - column 35, line 13 & WO 96 19463 A 27 June 1996 (1996-06-27). cited in the application & EP 0 826 676 A 4 March 1998 (1998-03-04) cited in the application & EP 0 745 596 A 4 December 1996 (1996-12-04) cited in the application & US 5 945 539 A 31 August 1999 (1999-08-31) cited in the application</p>	1,2,5, 11-13, 20-23
A	<p>WO 01 45703 A (NITROMED INC) 28 June 2001 (2001-06-28) page 1, lines 8-20; page 94, line 30 - page 104, line 4; examples 1, 2, 4-6, 8, 9, 18-20</p>	1,11-23
Y	<p>WO 02/30866 A (NICOX SA) 18 April 2002 (2002-04-18) example 10</p>	1,2,5,8, 11-13, 16-23
Y	<p>WO 96/13483 A (MERCK FROST CANADA INC) 9 May 1996 (1996-05-09) cited in the application page 8, line 4 - page 14, line 21; table II, compound 1 & EP 0 788 467 A 13 August 1997 (1997-08-13) cited in the application & US 5 849 943 A 15 December 1998 (1998-12-15) cited in the application</p>	1,2,5,8, 11-13, 16-23
Y	<p>WO 99/11605 A (NOVARTIS AG) 11 March 1999 (1999-03-11) cited in the application page 25, table 1, example 6; claims 1, 3-8</p>	1,2,5, 11-13, 19-23

INTERNATIONAL SEARCH REPORT

International Application No.
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Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

see additional sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☒ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claim 1 relates to an extremely large number of possible compounds. In fact, the claim contains so many options, variables and provisos that a lack of clarity (and conciseness) within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claim impossible. The search has been guided by those parts of the application which do appear to be sufficiently clear (and concise), namely examples 1-5 and claims 2-10. The search has mainly related to compounds of formula I, wherein

M-T = is the residue of a COX-2 selective inhibitor as defined in claim 5
b0 = 0 and c0 = 1;
TC = as defined in claim 1;
Y = d) -R10-, in which R1 is straight or branched C1-C6 alkylene (cf. claim 1 vs. claim 2), e) as defined in claim 2 or g) as defined in claim 2.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

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